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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/738,413	12/17/2003	Ralph R. Binetti	SC66U-US	8915

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EXAMINER	
BOWMAN, AMY HUDSON	
ART UNIT	**PAPER NUMBER**
1635	
MAIL DATE	**DELIVERY MODE**
12/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/738,413	BINETTI ET AL.	
	Examiner	Art Unit	
	Amy H. Bowman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/9/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed 10/9/07 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 7/10/07 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-39 are pending in the instant application.

This application contains subject matter in the claims that is not directed to the elected sequences, SEQ ID NOs: 1 and 2, which is drawn to an invention nonelected without traverse in the reply filed on 8/22/05. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant's arguments and/or amendments filed 10/9/07 have been fully considered but are not persuasive, as explained below.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 10/9/07 has been considered by the examiner.

Response to Arguments--Claim Rejections - 35 USC § 112, first paragraph

Claims 1-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for the reasons of record as set forth in the office actions mailed on 3/30/07 and 7/10/07.

Applicant argues that the unpredictability associated with the in vivo delivery of siRNAs alleged by the examiner does not reflect the state of the art as of applicant's filing date because the references are from 2000 and 2003. Applicant asserts that 2000 references dos not reflect the state of the art because it was published three years prior to the instant filing date. Contrary to applicant's assertion, the same delivery challenges remain regarding siRNA duplexes, as evidenced by Caplen (2003) and Zhang (2004). If delivery challenges had been eliminated in the art, then it would be improper to cite the Caplen (2000) reference. However, delivery challenges remained at the time that the instant application was filed and continue to be problematic to date, rendering a broad method of delivering a siRNA molecule to treat such a vast breadth of disorders unpredictable. Applicant argues that Caplen (2003) supports that the successful delivery and use both in vitro and in vivo of siRNA was routine. It is agreed that successes have been accomplished in delivering siRNAs in vitro and in vivo, as demonstrated by Caplen et al. (2003). It is not disputed that progress has been made between 2000 and 2003. The issue is the breadth of the instant claims. The specific successes reported by Caplen et al. do not enable a broad method of delivering a siRNA with a resultant treatment effect of treating any hyperpigmentation or any other unwanted pigmentation associated with the production of melanin. Neither the art or the

instant specification have demonstrated that administering a siRNA that is specific for mouse and human tyrosinase would result in treating such a vast breadth of disorders. Applicant argues that the statements of Caplen (2003) regarding delivery remaining a challenge for in vivo applications of siRNA and that many of the problems associated with RNAi as an effective therapeutic are the same as those encountered with previous gene therapy approaches do not negate the substance of the article which discusses the vast strides that RNAi has made and the successes in vivo. Contrary to applicant's assertions, the statements of Caplen (2003) regarding the fact that delivery remains to be an issue for siRNA in vivo are critical, as Caplen reports successes and still points out that delivery is an issue, supporting the examiner's position that specific successes have advanced the field of RNAi but have not enabled a broad method of treating such a broad genus of disorders as instantly recited, absent evidence to the contrary. The successes of Caplen (2003) support that there are enabled embodiments of in vivo delivery of siRNA molecules. These embodiments are not commensurate in scope with the instant claims. Applicant is relying on exemplifications of Caplen (2003) that are not representative of topical delivery of a siRNA specific for human and mouse tyrosinase with the broad treatment effect of treating any hyperpigmentation or any unwanted pigmentation associated with production of melanin.

Applicant cites Behlke for documenting the success of siRNA in vivo through a discussion of more than 90 publications which describe the successful use of RNAi in vivo spanning the years of 2002-2006, some of successes involving topical administration. Importantly, it is noted that applicant has not provided a particular model

that is recognized as correlating siRNA oligomers specific for mouse and human tyrosinase mRNA to the desired effect on the broad genus of conditions that are instantly recited. Although applicant continually argues in vivo delivery, which is an aspect of the enablement rejection, the paramount concern is that specification is not enabled for delivering a siRNA with the broad treatment effects that are instantly recited.

Regarding Behlke, and similar to Caplen (2003), as discussed above, it is acknowledged that there are many successful cases of in vivo delivery of siRNA molecules. However, in order for the instant claims to be enabled over the scope of the instant claims, there must be evidence that a siRNA that is specific for both mouse and human tyrosinase administered topically would have the desired outcome of treating any hyperpigmentation or any unwanted pigmentation associated with production of melanin. Absent such evidence, practicing the instant method would require undue experimentation for one of ordinary skill in the art.

Applicant refers to numerous studies referred to by Behlke and concludes that this is ample evidence that the use of siRNA in vivo is not generally unpredictable, as the examiner suggests. Importantly, not one of these successful in vivo exemplifications is commensurate in scope with the instant claims. Each of the successes represents an enabled embodiment of delivering siRNA molecules in vivo. However, it is acknowledged in the art that despite some successes, delivery broad delivery remains to be a challenge, as evidenced by such statements by Caplen (2003), for example. Behlke also discusses the necessity for further research regarding broad in vivo delivery and concludes "Although some labs have reported success using in vivo

administration of naked siRNAs, a greater number of investigators reported that using some kind of delivery system improved results. Route of administration and choice of which delivery tool to use will be crucial to success. Other than hydrodynamic delivery, too few in vivo studies have been published using any other single method to accumulate the amount of information needed to assess functional performance adequately or permit a general endorsement of the method, although several approaches do seem quite promising." Behlke is evidence that even post-filing (2006), route of administration and assessing the functional performance of each specific method remains to be paramount to the success of any given method of utilizing a siRNA in vivo.

Applicant argues that the Zhang et al. (2004) reference of record reports successful delivery via high-pressure tail vein injection of a siRNA. Again, the teachings of Zhang et al. are not commensurate in scope with the instant broad method. Applicant's arguments regarding each reference seem to be based on the position that if the reference teaches any specific successes, statements in the reference regarding delivery remaining to be a challenge in vivo are irrelevant. To the contrary, each of the references may teach enabled in vivo delivery of siRNA embodiments but disclose statements that delivery in general is still a major obstacle, particularly when desiring a specific therapeutic effect. As explained above, it is agreed that there are many successes in the field regarding targeting specific genes with specific siRNA molecules in vivo via a specific mode of administration and achieving a therapeutic result. However, the instant claims are directed to topically administering a siRNA specific for

mouse and human tyrosinase and achieving the desired outcome of treating any hyperpigmentation or any other unwanted pigmentation associated with the production of melanin. However, nothing in the art of the instant specification enables such a broad method of delivering a siRNA topically that is specific for human and mouse tyrosinase and achieving such a broad therapeutic effect.

Next, applicant cites Wraight et al. (2000) and Mehta et al. (2000) for supporting successful topical delivery of oligonucleotides. Importantly, it is not disputed if topical oligonucleotides penetrate the epidermis of the skin, as argued by applicant. It is disputed if delivering a siRNA topically that is specific for human and mouse tyrosinase would result in such a broad therapeutic effect without undue experimentation. Neither Wraight et al. or Mehta et al. address the delivery of siRNA molecules or correlate inhibiting human and mouse tyrosinase with any hyperpigmentation or any other unwanted pigmentation associated with the production of melanin.

Applicant argues that Hartmann et al. (2004) of record teaches that the pathophysiology of hypopigmentary disorders is still poorly understood, but the instant claims are directed to hyperpigmentary disorders, not hypopigmentary disorders. Contrary to applicant's assertion, Hartmann et al. supports that disorders within the instant scope of the instant claims are still poorly understood, post-filing, and therefore support that there is not necessarily a correlation between inhibiting human and mouse tyrosinase and treating any hyperpigmentation or any unwanted pigmentation associated with the production of melanin. Applicant argues that "unwanted pigmentation associated with the production of melanin" is the opposite of

hypopigmentary. However, hypopigmentary disorders meet the instant limitation of being an unwanted pigmentation and hypopigmentary disorders can certainly be associated with the production of melanin. A lack of production of melanin is certainly associated with the production of melanin. Furthermore, applicant has not offered any evidence of a correlation between inhibiting human and mouse tyrosinase with treating such a vast breadth of disorders.

MPEP 2164.01
Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, **when filed**, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention.

Also, MPEP 2164.01(a)
A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, **at the time the application was filed**, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

A conclusion of lack of enablement means that the specification, **at the time the application was filed**, would not have taught one skilled in the art how to make and/or use the **full scope** of the claimed invention without undue experimentation (see MPEP 2164.01(a)).

MPEP 2164.08 explains that the questions of enablement are evaluated against the claimed subject matter and the focus of the examination inquiry is whether **everything** within the scope of the claim is enabled. Applicant is claiming treatment effects of any hyperpigmentation or any unwanted pigmentation associated with the production of melanin via topically administering any siRNA oligomer specific for mouse and human tyrosinase. The specification is not enabling for treatment, amelioration,

reduction and/or elimination of such a vast genus of disorders via topically administering such a broad genus of siRNA oligomers.

Response to Arguments--Claim Rejections - 35 USC § 112

Claims 1-3 and 5-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Applicant argues that the sequences for both mouse and human tyrosinase have been known in the art for many years and therefore applicants are not required to reproduce them in the application. Although applicant points to gi:340039 for human tyrosinase and gi:202249 for mouse tyrosinase, the instant claims are not closed to these sequences. The instant claims are directed to administering only those siRNA molecules that target both mouse and human tyrosinase, although applicant has not closed mouse or human "tyrosinase" to any single sequence in the claims.

The instant specification discloses three sequences that are "homologous to sequences found in both human and mouse forms of tyrosinase". It is noted that although applicant is claiming a method involving only the specific subset of siRNAs that target both mouse and human tyrosinase mRNA, the human and mouse mRNA sequences have not been defined by applicant in a way that would allow for one of ordinary skill to envision which siRNA oligomers are directed to both sequences without further knowledge of the sequences because "tyrosinase", as instantly claimed can encompass any mouse or human tyrosinase sequence, as well as encompass any mouse or human tyrosinase homolog or allele known or yet to be discovered of mouse

or human tyrosinase, as well as DNA genomic fragments, spliced variants or fragments that retain mouse or human tyrosinase-like activity.

For example, applicant refers to a human tyrosinase sequence by GenBank sequence identification no. gi: 340039, which is 1929 bases in length, whereas Bennett et al. (US 2004/0215006 A1) refers to human tyrosinase by GenBank accession number M27160.1, which is 2384 nucleotides in length.

One of ordinary skill in the art could not envision the member siRNAs of the instant method that are targeted to both human and mouse tyrosinase mRNA without knowledge of the target sequences in order to define which area of the sequences are homologous and which are not. Therefore, one would not be able to recognize that the applicant was in possession of the claimed genus at the time of filing.

Response to Arguments---Claim Rejections - 35 USC § 102

Claims 1-3, 5-9, 14-25 and 31 are rejected under 35 U.S.C. 102(e) as being anticipated by Bennett et al. (US 2004/0215006 A1).

As explained in the office action mailed on 7/10/07, Bennett et al. is considered as enabled as the instant specification. Bennett et al. is applied as teaching the instant method although the teachings of Bennett et al. regarding in vivo effects are prophetic and are considered as enabled as the instant claims, consistent with the rejection of the instant claims under 35 U.S.C. 112, first paragraph, explained above.

Applicant argues that Bennett et al. discloses oligomers that target human or mouse tyrosinase mRNA, but not those target both. Contrary to applicant's assertion, although Bennett et al. disclose a table of oligonucleotides that target human tyrosinase and a table of oligonucleotides that target mouse tyrosinase, the oligonucleotides are not mutually exclusive. Since there is an overlap in the human and mouse target sequences disclosed by Bennett et al., oligonucleotides targeted to the human sequence many target the mouse sequence as well.

For example, Bennett et al. disclose that duplexes of the invention comprise an antisense strand that comprises at least a portion of an oligonucleotide in Table 1 (see Example 5, page 14). Table 1 discloses multiple oligonucleotides, or antisense strand sequences, that target a human tyrosinase sequence, but are not disclosed as not targeting the mouse sequence as well. For example, SEQ ID NO: 27 in Table 1 of Bennett et al. is 20 nucleotides in length and targets the human tyrosinase sequence disclosed by Bennett et al. at position 1609. This oligonucleotide targets both the human and mouse sequences disclosed by Bennett et al. (starting at position 1609 of the human sequence disclosed as GenBank M27160.1 by Bennett et al. and starting at position 1168 of the mouse sequence disclosed as GenBank NM_011661.1 by Bennett et al; position 1609 of the human sequence of Bennett et al. corresponds to position 1147 of the human sequence referred to in applicant's arguments filed on 10/9/07 (GenBank 340039), whereas the mouse sequence is the same). Therefore, although Bennett et al. lists oligonucleotide sequences in a human table and in a mouse table, Bennett et al. discloses oligonucleotides that may target both sequences and teaches

that duplexes of the invention comprise the sequences or portions of the sequences in table 1. Neither Bennett et al. nor the instant specification disclose a structure to define which molecules would be targeted to both sequences. However, Bennett et al. discloses the specific human and mouse sequences that are being referred to and disclose oligonucleotides such as SEQ ID NO: 27 that are complementary to both.

Therefore, the instant invention is anticipated by Bennett et al.

Response to Arguments--Claim Rejections - 35 USC § 103

Claims 1-3 and 5-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bennett et al. (US 2004/0215006 A1), in view of Mahashabde et al. (US 6,436,378 B1), and Perricone (US 2002/0141956 A1).

Applicant has not offered any arguments regarding this rejection that have not been directly addressed in the rejection under 35 U.S.C. 102 (Bennett et al.) above. Applicant asserts that Mahashabde and Perricone do not teach the use of siRNA oligomers in the instant method and therefore do not rectify the deficiencies of Bennett. Mahashabde and Perricone were not relied upon for teaching methods of utilizing siRNA oligomers and Bennett et al. is relied upon as explained in the rejection under 35 U.S.C. 102 above.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is (571) 272-0755. The examiner can normally be reached on Monday-Thursday 6:30 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Examiner
Art Unit 1635

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